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The Sequence of Cyclophosphamide and Myeloablative Total Body Irradiation in Hematopoietic Cell Transplantation for Patients with Acute Leukemia

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A B S T R A C T

Limited clinical data are available to assess whether the sequencing of cyclophosphamide (Cy) and total body irradiation (TBI) changes outcomes. We evaluated the sequence in 1769 (CyTBI, n = 948; TBICy, n = 821) recipients of related or unrelated hematopoietic cell transplantation who received TBI (1200 to 1500 cGY) for acute leukemia from 2003 to 2010. The 2 cohorts were comparable for median age, performance score, type of leukemia, first complete remission, Philadelphia chromosome–positive acute lymphoblastic leukemia, HLA-matched siblings, stem cell source, antithymocyte globulin use, TBI dose, and type of graft-versus-host disease (GVHD) prophylaxis. The sequence of TBI did not significantly affect transplantation-related mortality (24% versus 23% at 3 years, $P = .67$; relative risk, 1.01; $P = .91$), leukemia relapse (27% versus 29% at 3 years, $P = .34$; relative risk, .89, $P = .18$), leukemia-free survival (49% versus 48% at 3 years, $P = .27$; relative risk, .93; $P = .29$), chronic GVHD (45% versus 47% at 1 year, $P = .39$; relative risk, .9; $P = .11$), or overall survival (53% versus 52% at 3 years, $P = .62$; relative risk, .96; $P = .57$) for CyTBI and TBICy, respectively. Corresponding cumulative incidences of sinusoidal obstruction syndrome were 4% and 6% at 100 days ($P = .08$), respectively. This study demonstrates that the sequence of Cy and TBI does not impact transplantation outcomes and complications in patients with acute leukemia undergoing hematopoietic cell transplantation with myeloablative conditioning.
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INTRODUCTION

Controversy concerning the optimal conditioning regimen and sequence of modalities for patients with hematologic malignancies still persists. The optimal regimen would maximize tumor cell kill and minimize toxicities. Cyclophosphamide (Cy) and total body irradiation (TBI) have

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been used in combination as a preparative regimen for high-risk hematologic malignancies for several decades. Animal preclinical data in the early 1990s showed that Cy given 24 hours after TBI (TBICy) caused less lung damage but more bone marrow damage in the murine model [1,2]. Lowenthal et al. showed that the reverse, or CyTBI, offers an improved antileukemic effect, compared with TBICy, in mice with B cell leukemia/lymphoma [3]. The optimal sequence of these agents in the preparative regimen and the associated impact on clinical outcomes, such as transplantation-related mortality (TRM) and leukemia relapse, has not been systematically studied to date.

Synergism between chemotherapy and radiation therapy exists. In early studies, TBI was used solely as the conditioning regimen [4]. The goal of TBI is to obliterate the host marrow, deplete residual leukemia, and allow for donor marrow cells to repopulate through immune-ablation. TBI has high efficacy; however, there is controversy over the optimal dose, as higher doses have been related to increased incidence of graft-versus-host disease (GVHD) and mortality, thought to be triggered by radiation-related tissue damage [5]. A TBI-only regimen was less effective at lower doses of TBI and more toxic at higher doses of TBI (1400 to 2000 cGy) [6]. Cy was later added to the regimen, permitting lower TBI doses to be used, thereby decreasing the incidence of pulmonary toxicity while maintaining stable rates of leukemia relapse and immune-ablation [7]. The standard regimen for adults used for disease ablation and immunosuppression in patients with leukemia was established in the early 1970s and is Cy 60 mg/kg/day for 2 days for adults (4 days for children) followed by 3 to 4 days of TBI [7]. A number of modifications to this regimen have been introduced to improve the rates of engraftment and reduce the relapse rate and radiation complications [8,9]. Another rationale for changing the sequence in the conditioning regimens was related to Cy-induced emesis, which could affect the scheduling of subsequent TBI. Despite evidence that CyTBI is a good choice of myeloablative regimen, no overall consensus on timing of TBI and Cy has been investigated in large series.

This is a common clinical question in cases of conflicting schedules of irradiation treatment days and arrival or availability of a stem cell product for transplantation. The goal of this study was to compare CyTBI to TBICy in terms of the incidence of GVHD, leukemia relapse, and incidence of sinusoidal obstruction syndrome (SOS).

METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive hematopoietic cell transplantations to a statistical center located at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program Coordinating Center in Minneapolis. Participating centers are required to report all transplantations consecutively; compliance is monitored by onsite audits. The CIMBTR maintains an extensive database of detailed patient-, transplantation-, and disease-related information, and prospectively collects data longitudinally with yearly follow-ups. Observational studies conducted by the CIBMTR are performed in compliance with Health Insurance Portability and Accountability Act regulations as a public health authority and also in compliance with all applicable federal regulations pertaining to the protection of human research participants, as determined by a continuous review by the institutional review boards of National Marrow Donor Program and the Medical College of Wisconsin [10].

Patients

Patients were younger than 60 years, received hematopoietic cell transplantation with Cy and TBI with myeloablative doses of 1200 to 1500 cGY for treatment of acute leukemia in first or second complete morphologic remission from 2003 to 2010, and reported to the CIBMTR. Patients who received umbilical cord blood grafts, haploidentical or other HLA-mismatched donors, or ex vivo T cell depletion were excluded. Median follow-up of cohort was 56 months and the completeness index [11] (the observed/the expected follow-up) for a 3-year analysis was 88%. Eligible patients were separated according to the sequence of agents into CyTBI and TBICy groups based on the reported dates of administration of Cy and TBI.

Outcome

The conditioning regimen sequence was compared according to overall survival (OS), leukemia-free survival (LFS), TRM, leukemia relapse, GVHD, and SOS. Events of GVHD and SOS were defined by transplantation centers. GVHD data included date of onset, organ involvement, and maximum grade. SOS data includes differential diagnosis and supporting clinical and diagnostic information. *OS* was defined as death by any cause and patients were censored at time of last follow-up. Leukemia relapse or death was recorded as the event for the LFS outcome. *TRM* was defined as any death in the absence of prior leukemia relapse. GVHD was analyzed as grades III and IV and II to IV acute (aGVHD) according to modified Gluksberg [12] and chronic GVHD (cGVHD).

Statistical Analysis

Eligible patients were separated into 2 cohorts according to the sequence of TBI and Cy (CyTBI and TBICy), defined according to date of initiation of each component of the conditioning regimen. Selected variables were described for both cohorts, continuous variables were compared by Kruskall Wallis test, and categorical variables by chi-square test to assess significant differences (defined as P value $< .05$).

Survival outcomes including OS and LFS were computed using Kaplan-Meier and comparison was done with log rank test. For leukemia relapse, TRM and GVHD outcomes, and SOS incidence, cumulative incidence was used to account for competing risks. Cox proportional hazards regression models for overall mortality, treatment failure (inverse of LFS), relapse and TRM were built using a forward selection approach forcing the main effect covariates (TBICy versus CyTBI) on all outcomes. The covariates analyzed include age, gender, performance score, donor-recipient gender, disease and disease status, cytogenetic risk stratification (for acute myeloid leukemia (AML) according to the Southwest Oncology Group/Eastern Cooperative Oncology Group classification [13]: favorable, intermediate, poor, or unknown; for acute lymphoid leukemia (ALL): presence of Philadelphia chromosome [Ph+], Ph negative and Ph status unknown), year of transplantation, donor type (sibling, well matched, and partially matched unrelated donor) [14], dose of TBI (12 Gy versus 13 Gy), donor recipient cytomegalovirus status, graft source, in vivo T cell depletion. Disease status and cytogenetic assessments were performed at the transplantation center and reported to the CIBMTR. The final model included all covariates significantly associated with the outcome ($P < .05$) and the main effect. Test for proportional hazards was included in case of nonproportional hazards during the study period and test for interactions was done between the main effect covariates and all significant covariates in each model.

RESULTS

Demographics

A total of 948 patients received CyTBI and 821 received TBICy. The 2 cohorts were comparable for patient-, disease-, and transplantation-related characteristics (Table 1) with the exception of age and Cy dose. The median age was 33 in the CyTBI group and 35 in the TBICy group ($P < .01$). The median Cy dose was 108 mg/kg in the CyTBI group and 115 mg/kg in the TBICy group ($P = .01$). The median interval between starting TBI and Cy was 2 and 4 days for CyTBI and TBICy, respectively.

GVHD

Cumulative incidences of grade II to IV aGVHD at day 100 were 39% (95% confidence interval [CI], 35% to 42%) and 45% (95% CI, 41% to 48%; $P = .01$), and of grades III and IV aGVHD were 16% (95% CI, 13% to 18%) and 15% (95% CI, 12% to 17%; $P = .60$) for CyTBI and TBICy, respectively (Figure 1). Multivariate analysis comparing CyTBI to TBICy demonstrated a relative risk for grades II to IV aGVHD of .87 (95% CI, .75 to 1.00; $P = .05$) and for grades III and IV aGVHD of 1.09

Table 1
Characteristic of AML and ALL Patients who Received Allogeneic Hematopoietic Cell Transplantation with TBI and Cy Conditioning Regimen between 2003 and 2010, According to Sequence of Administration

Characteristics of Patients	TBICy	CyTBI	*P* Value
No. of patients	821	948	
No. of centers	100	114	
Age, median (range), yr	33 (2-60)	35 (2-60)	<.01
0-9	64 (8)	61 (6)	<.01
10-19	147 (18)	114 (12)	
20-29	157 (19)	212 (22)	
30-39	168 (20)	172 (18)	
40-49	180 (22)	224 (24)	
50-59	105 (13)	165 (17)	
Sex			.63
Male	458 (56)	518 (55)	
Female	363 (44)	430 (45)	
Race			.01
Caucasian	663 (81)	827 (87)	
African-American	30 (4)	31 (3)	
Asian	76 (9)	49 (5)	
Pacific islander	2 (<1)	1 (<1)	
Native American	5 (<1)	4 (<1)	
Other	20 (2)	14 (1)	
Unknown	25 (3)	22 (2)	
Performance score			.08
<90%	164 (20)	223 (24)	
≥90%	608 (74)	656 (69)	
Unknown	49 (6)	69 (7)	
Disease			.09
AML	456 (56)	489 (52)	
ALL	365 (44)	459 (48)	
AML/ALL disease status before transplantation			.82
First CR	529 (64)	606 (64)	
Second CR	292 (36)	342 (36)	
AML cytogenetics			.55
Favorable	36 (8)	44 (9)	
Intermediate	187 (41)	187 (38)	
Poor	105 (23)	129 (26)	
Unknown	128 (28)	129 (26)	
ALL Ph+			.77
No	131 (36)	154 (34)	
Yes	90 (25)	115 (25)	
Unknown	144 (39)	190 (41)	
Donor/recipient HLA match			.01
HLA-identical sibling	281 (34)	329 (35)	
Well-matched URD	346 (42)	450 (47)	
Partially matched URD	136 (17)	125 (13)	
URD-HLA matching unavailable	58 (7)	44 (5)	
Graft type			.12
BM	305 (37)	319 (34)	
PB	516 (63)	629 (66)	
Donor/recipient sex match			.62
M-M	291 (35)	333 (35)	
F-M	165 (20)	180 (19)	
M-F	194 (24)	241 (25)	
F-F	168 (20)	186 (20)	
Unknown	3 (<1)	8 (<1)	
Donor-recipient CMV status			.35
+/+	224 (27)	272 (29)	
+/−	96 (12)	122 (13)	
−/+	203 (25)	250 (26)	
−/−	266 (32)	264 (28)	
Unknown	32 (4)	40 (4)	
Total Cy dose, median (range), mg/kg	115 (<1-470)	108 (<1-486)	.01
<55 mg/kg	33 (4)	58 (6)	.02
55-96 mg/kg	166 (20)	234 (25)	
97-120 mg/kg	474 (58)	482 (51)	
121-135 mg/kg	52 (6)	70 (7)	
>135 mg/kg	28 (3)	39 (4)	
Unknown	68 (8)	65 (7)	
TBI dose			.51
1200-1300 cGy	514 (63)	579 (61)	
1320-1500 cGy	307 (37)	369 (39)	
TBI fractionated			.21
No	1 (<1)	4 (<1)	
Yes	820 (99)	942 (99)	
Unknown	0	2 (<1)	
CNS boost given			.40
No	768 (94)	891 (94)	
Yes	52 (6)	53 (6)	
Unknown	1 (<1)	4 (<1)	
Interval between TBI and Cy, d	4 (2-7)	2 (2-6)	<.001
Year of transplantation			.08
2003	67 (8)	78 (8)	
2004	130 (16)	167 (18)	
2005	118 (14)	173 (18)	
2006	137 (17)	142 (15)	
2007	107 (13)	110 (12)	
2008	103 (13)	84 (9)	
2009	85 (10)	98 (10)	
2010	74 (9)	96 (10)	
Use of ATG			.10
ATG alone	108 (13)	101 (11)	
No ATG	713 (87)	847 (89)	
GVHD prophylaxis			.12
Tacro + MMF ± others	57 (7)	70 (7)	
Tacro + MTX ± others	371 (45)	409 (43)	
Tacro ± others	42 (5)	76 (8)	
CSA + MMF ± others	11 (1)	5 (<1)	
CSA + MTX ± others	317 (39)	364 (38)	
CSA ± others	15 (2)	13 (1)	
Other GVHD prophylaxis	8 (<1)	11 (1)	
Follow-up of survivors, median (range), mo	57 (3-100)	56 (3-100)	

CR indicates complete remission; URD, unrelated donor; BM, bone marrow; PB, peripheral blood; M, male; F, female; CMV, cytomegalovirus; CNS, central nervous system; ATG, antithymocyte globulins; Tacro, tacrolimus; MMF, mycophenolate mofetil; MTX, methotrexate; CSA, cyclosporine.

(95% CI, .86 to 1.38; $P = .50$). Other covariates associated with grades II to IV aGVHD were donor-recipient gender combinations, donor type, and graft source (Supplementary Table A). Donor type and year of transplantation were associated with grades III and IV aGVHD.

The cumulative incidences of cGVHD at 1 year were 45% (95% CI, 41% to 48%) and 47% (95% CI, 43% to 50%; $P = .39$) (Figure 1). Multivariate analysis of cGVHD the relative risk of CyTBI was .9 (95% CI, .79 to 1.03; $P = .11$). Other covariates associated with cGVHD were donor recipient gender match, donor type, and graft source.

Leukemia Relapse and TRM

The cumulative incidences of leukemia relapse at 3 years were 27% (95% CI, 24% to 30%) and 29% (95% CI, 26% to 33%; $P = .34$) for CyTBI and TBICy, respectively (Figure 2). Corresponding cumulative incidences for TRM at 3 years were 24% (95% CI, 21% to 27%) and 23% (95% CI, 20% to 26%; $P = .67$). Multivariate analyses for leukemia relapse and TRM with associated covariates are shown in Table 2.

SOS

Cumulative incidences for SOS at 100 days were 4% (95% CI, 3% to 6%) and 6% (95% CI, 4% to 8%; $P = .08$) with CyTBI and TBICy, respectively.

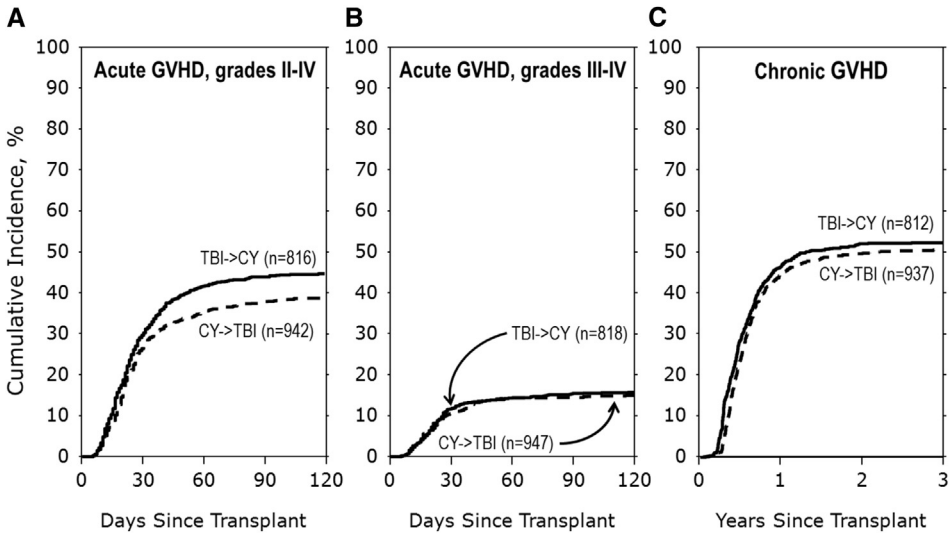

Figure 1. Cumulative incidences of II to IV (A) and III and IV (B) acute GVHD, and chronic GVHD (C) comparing CyTBI with TBICy before allogeneic transplantation for acute leukemia.

LFS and OS

Three-year probabilities of LFS were 49% (95% CI, 46% to 52%) and 48% (95% CI, 44% to 51%; $P = .34$) for CyTBI and TBICy, respectively (Figure 2). Corresponding 3-year probabilities of OS were 53% (95% CI, 50% to 57%) and 52% (95% CI, 49% to 56%; $P = .48$). Multivariate analyses for treatment failure (1-LFS) and overall mortality with associated covariates are shown in Table 2. OS by different subset of children, adults, and patients with ALL and AML are shown in Figure 3.

Causes of Death

There was a wide range of causes of death for patients in each group, with the most common causes being leukemia relapse, infection, GVHD, and pulmonary failure. Causes of death were comparable between both treatment groups (Supplementary Table B).

DISCUSSION

This large retrospective analysis study compared the sequence of TBI and Cy in the myeloablative conditioning intensity setting for acute leukemia. Transplantation outcomes were generally similar regardless of the sequence of TBI, with exception of grades II to IV aGVHD. All the outcomes were similar when separating the cohort by disease (AML and ALL) and by patient populations (children and adults).

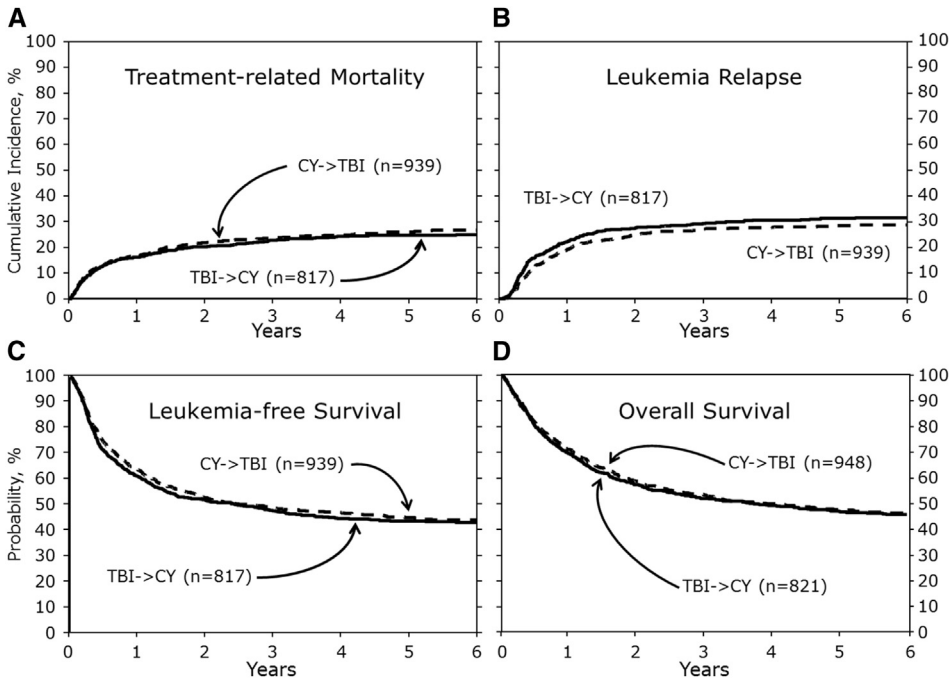

Figure 2. Cumulative incidence of transplantation-related mortality (A), cumulative incidence of leukemia relapse (B), probability of leukemia-free survival (C), and probability of overall survival (D) comparing CyTBI with TBICy before allogeneic transplantation for leukemia.

Table 2
Multivariate Analysis of TRM, Leukemia Relapse, Treatment Failure, and Overall Mortality Comparing CyTBI to TBICy and Additional Covariates Associated with Each Outcome

TRM	n	RR (95% CI)	*P* Value
Main effect			.91*
TBI/Cy	817	1.00	–
Cy/TBI	939	1.01 (.84-1.23)	
Other covariates			
Age			<.0001*
0-9	124	1.00	–
10-19	260	2.49 (1.21-5.14)	.013
20-29	364	3.02 (1.57-5.83)	.0010
30-39	337	4.27 (2.21-8.24)	<.0001
40-49	401	5.01 (2.61-9.62)	<.0001
50-59	270	6.09 (3.15-11.80)	<.0001
Donor-recipient sex match			<.0001*
M-M	621	1.00	–
F-M	343	1.40 (1.09-1.80)	.0088
M-F	433	.66 (.50-.87)	.0028
F-F	348	1.18 (.91-1.51)	.21
Performance score			.0025*
<90%	383	1.00	–
90%-100%	1256	.70 (.56-.87)	.0012
Unknown	117	.96 (.65-1.43)	.85
Donor type			<.0001*
HLA-identical sibling	607	1.00	–
Well-matched URD	786	1.53 (1.22-1.94)	.0003
Partially matched URD	261	2.62 (1.99-3.44)	<.0001
URD-HLA match missing	102	1.13 (.71-1.81)	.60
Leukemia relapse			
Main effect			.18*
TBI/Cy	817	1.00	–
Cy/TBI	939	.89 (.75-1.06)	.18
Other covariates			
Cytogenetics			<.0001*
AML intermediate	374	1.00	–
AML favorable	80	.14 (.05-.31)	<.0001
AML unfavorable	234	1.61 (1.20-2.16)	.001
AML unknown	256	1.08 (.79-1.47)	.22
ALL Ph neg	285	1.16 (.86-1.56)	.34
ALL Ph+	205	1.20 (.85-1.68)	.30
ALL Ph unknown	334	1.31 (.99-1.74)	.055
Disease status before transplantation			.0016*
First CR	1125	1.00	–
Second CR	631	1.34 (1.12-1.61)	.0016
Treatment failure			
Main effect	817		.29*
TBI/Cy	939	1.00	–
Cy/TBI		.93 (.82-1.06)	.29
Other covariates			
Age			<.0001*
0-9	124	1.00	–
10-19	260	1.52 (1.07-2.15)	.020
20-29	364	1.54 (1.12-2.11)	.0072
30-39	337	1.90 (1.37-2.62)	.0001
40-49	401	1.98 (1.43-2.74)	<.0001
50-59	270	2.48 (1.78-3.47)	<.0001
Donor-recipient sex match			.0005*
M-M	621	1.00	–
F-M	343	1.14 (.95-1.36)	.15
M-F	433	.77 (.65-.92)	.0044
F-F	348	1.05 (.88-1.25)	.62
Performance score			.0007*
<90%	383	1.00	–
90%-100%	1256	.78 (.67-.91)	.0015
Unknown	117	1.08 (.82-1.40)	.60
Cytogenetics			.0012
AML intermediate	374	1.00	–
AML favorable	80	.51 (.34-.79)	.002
AML unfavorable	234	1.26 (1.01-1.58)	.04
AML unknown	256	1.10 (.88-1.37)	.40
ALL Ph neg	285	1.20 (.96-1.51)	.10
ALL Ph+	205	1.31 (1.03-1.67)	.03
ALL Ph unknown	334	1.18 (.96-1.47)	.12
Disease status before transplantation			.0081*
First CR	1125	1.00	–
Second CR	631	1.22 (1.05-1.40)	.0081
Donor type			.0007*
HLA-identical sibling	607	1.00	–
Well-matched URD	786	1.15 (.99-1.35)	.070
Partially matched URD	261	1.45 (1.89-1.76)	.0002
URD-HLA match missing	102	.84 (.60-1.69)	.29
Overall mortality			
Main effect			.57*
TBI/Cy	821	1.00	–
Cy/TBI	948	.96 (.84-1.10)	.57
Other covariates			
Age			<.0001*
0-9	125	1.00	–
10-19	261	1.51 (1.05-2.19)	.027
20-29	369	1.65 (1.19-2.28)	.0028
30-39	340	2.05 (1.46-2.87)	<.0001
40-49	404	2.17 (1.54-3.04)	<.0001
50-59	270	2.84 (2.01-4.02)	<.0001
Donor-recipient sex match			.0002*
M-M	624	1.00	–
F-M	345	1.16 (.97-1.39)	.11
M-F	435	.76 (.63-.91)	.0035
F-F	354	1.05 (.87-1.26)	.61
Performance score			.0011*
<90%	387	1.00	–
90%-100%	1264	.76 (.65-.89)	.0008
Unknown	118	.99 (.75-1.31)	.97
Disease status before transplantation			.0022*
First CR	1135	1.00	–
Second CR	634	1.26 (1.09-1.46)	.0022
Donor type			<.0001*
HLA-identical sibling	610	1.00	–
Well-matched URD	796	1.13 (.96-1.33)	.13
Partially matched URD	261	1.57 (1.29-1.92)	<.0001
URD-HLA match missing	102	.83 (.58-1.18)	.30
Cytogenetics			.0023*
AML intermediate	374	1.00	–
AML favorable	80	.56 (.37-.86)	.009
AML unfavorable	234	1.35 (1.07-1.71)	.012
AML unknown	256	1.10 (.87-1.38)	.44
ALL Ph-neg	285	1.26 (1.00-1.59)	.048
ALL Ph+	205	1.26 (.98-1.63)	.068
ALL Ph- unknown	334	1.20 (.96-1.51)	.10

RR indicates relative risk.
* Overall *P* value.

A study by McDonald et al. linked circulating cyclophosphamide metabolites to liver dysfunction during TBI-based transplantation [15]. The metabolism of Cy was found to be highly variable, and increased levels of 1 of the metabolites, carboxyethyl–phosphoramide mustard, was correlated with higher rates of SOS and nonrelapse mortality [15]. Subsequently, a phase II trial investigated the effect of a personalized dosing scheme for each patient according to Cy pharmacokinetics [16]. The trial concluded that a personalized dosing system led to lower peak bilirubin levels and acute kidney injury; however, nonrelapse and OS rates were similar to controls [16]. These studies demonstrate a variability of Cy exposure using a standard regimen and a common protocol. Altering the sequence of specific agents may increase the variability of Cy metabolism and deserves to be specifically tested.

The exact timing between each component of the conditioning regimen may also influence toxicity and transplantation outcomes. Hassan et al. compared outcomes

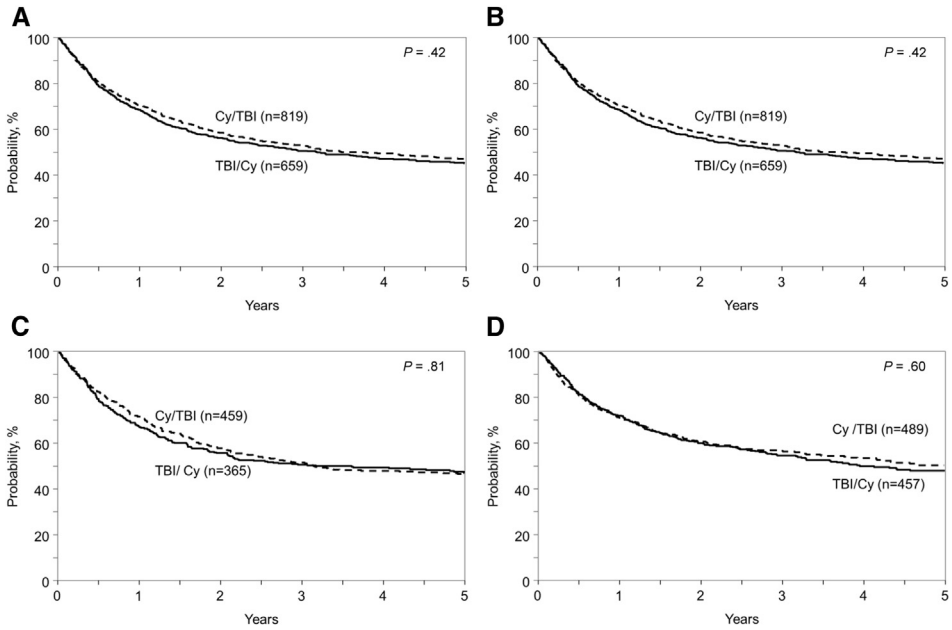

Figure 3. Overall survival among (A) adults patients, (B) children, (C) patients with acute lymphoid leukemia, and (D) with acute myeloid leukemia according to the sequence of cyclophosphamide and total body irradiation as part of a myeloablative conditioning before allogeneic hematopoietic cell transplantation.

according to time between the last dose of busulfan and Cy and demonstrated that shorter intervals (<24 hours) were associated to higher exposure to Cy and, consequently, more toxicities [17]. In preclinical studies, shorter intervals between irradiation and chemotherapy were also associated with higher irradiation-induced tissue damage [18-19]. The present study could only address the sequence of agents, as only the date of initiation of each agent was available. The interval of initiation of each agent was different between the groups, as TBI is usually administered over a 3-day period and Cy over a 2-day period. Additionally, the interval distribution in both groups was narrow; thus, the interval between the first days of each agent is closely related to the sequence of agents.

Enhanced toxicity from TBI exposure to Cy metabolites could also theoretically contribute to aGVHD. When analyzing the incidence of aGVHD in both groups, we found that grade II to IV GVHD at 100 days after transplantation was significantly less in the CyTBI group. This should be interpreted with caution because the multivariate analysis showed borderline effect and there was no difference between the 2 approaches on grades III and IV aGVHD. Additionally, the dose of TBI was evaluated and it was not associated with the development of GVHD or any other outcomes analyzed.

We also show that the specific type of acute leukemia is not a factor in choosing a conditioning sequence. Previous studies have shown that differences exist in the preparative regimens for AML versus ALL. The optimal exact dosing of TBI has not been established; however, total doses of >13 Gy were associated with improved LFS, relapse, and mortality in ALL patients in second complete remission [20]. In contrast, Clift et al. were able to show decreased relapse but increased mortality in AML patients treated with higher doses of TBI [5].

Because our analysis is retrospective, it does have limitations, including the reason why 1 conditioning regimen sequence was chosen over the other. The specific sequence was not restricted to a number of transplantation centers and the majority of centers reported both sequences. This observation likely reflects practice, as changes in the sequence of agents are done to accommodate transplantation schedule and other activities during the timing of transplantation. Although ideally this question of the timing of preparative components would be answered in a randomized prospective trial, our data would support equipoise for these decisions at this juncture.

This large cohort study demonstrates that the sequence of Cy and TBI does not affect transplantation outcomes and survival in patients with acute leukemia undergoing myeloablative transplantation in terms of toxicity or antileukemia benefit. TBICy may offer an advantage for a shorter hospitalization because of possible TBI delivery in the outpatient setting. This could potentially reduce the psychological distress associated with prolonged hospitalization. Furthermore, the apparent lack of difference in outcomes on an exact sequence of these 2 conditioning regimen agents provides flexibility for transplantation planning.

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SUPPLEMENTARY DATA

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